Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 6-8, 10, 15-17, 25, 26, 36, 37 and 38 are pending in the application. Claims 1 and 6 are sought to be amended and new claims 37 and 38 are sought to be entered. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Applicants respectfully request that the Examiner enter these amendments after final. The amendments will not require an additional search or examination and put the application in better condition for allowance or appeal.

In the present Office Action, the Examiner indicates that claim 10 is not among the pending claims (see page 1, item number 4). However, claim 10 has not been canceled. See page 2 of the "Amendment and Reply Under 37 C.F.R. § 1.111" filed June 26, 2001. Clarification is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to Claim 6

The Examiner objected to claim 6 on the basis that it is dependent upon canceled claim 5.

In the "Amendment and Reply Under 37 C.F.R. § 1.111" filed June 26, 2001, Applicants attempted to amend claim 6 to make it dependent upon claim 1. See page 2. It appears that the amendment was not entered. Applicants have represented the amendment for the convenience of the examiner.

Withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner has maintained the rejection to claims 25 and 26 under 35 U.S.C. § 102(b) as being anticipated by Everitt *et al.*, *Experimental Cell Research 199(1):* 134-146 (March 1992). Applicants respectfully traverse the rejection.

According to the Examiner:

> Everett et al. teach that the vectors constructed are eukaryotic expression vectors (p. 136, ¶ bridging cols. 1 and 2, especially lns. 1-4). Therefore, even though Everett et al. use these vectors to transfer genetic material into a murine cell line, they would also be capable of transferring genetic material into human cells since human cells, like murine cells, are eukaryotic cells.
>
> In response to the argument that claim 25 now specifies an antisense polynucleotide that binds to and inhibits expression of <u>human</u> osteonectin mRNA, the fact that Everett et al. use the mouse ortholog of the human osteonectin transcript to construct the antisense sequence does not preclude it from being the human transcript. . . it is likely that the antisense construct of Everett et al. would be capable of binding to and inhibiting expression of the human sequence if expressed in a human cell.

Office Action at page 3, line 17, through page 4, line 16.

Applicants respectfully disagree. On page 136 (paragraph spanning columns 1 and 2), Everitt *et al.* describe eukaryotic expression vectors capable of generating SPARC and antisense SPARC mRNA that were constructed to over-express or inhibit the expression of

SPARC in undifferentiated F9 cells and their endodermal derivatives. As pointed out in Applicants' previous Reply, the F9 cell line is a *murine* embryonal carcinoma stem cell line.

Hence, Everitt *et al.* describe the construction of vectors specifically for use in undifferentiated F9 cells, a non-human cell line. The Examiner has suggested that these vectors would be suitable for transfer of genetic material into a human cell line because murine cells, like human cells, are eukaryotic. However, this is not the case as the vectors of Everitt *et al.* are stated as having been specifically constructed for use in murine F9 cells. There is no suggestion that these vectors are suitable in other eukaryotic cells, or even that the vectors could be used with human cells. In the absence of such a suggetion, it cannot properly be inferred that the eukaryotic expression vectors of Everitt *et al.* are capable of transferring genetic material into a human cell.

It is commonly known in the art that different vectors are used for different cells. Some vectors are more appropriately used with certain cell types and would not be successful with other cell types. It would not be logical for a person of skill in the art to assume that an eukaryotic expression vector constructed for use in a murine cell line would be suitable for use in a human cell line. In the absence of any teaching in that direction, the Examiner's conclusions with regards to the subject matter of the present Claim 25 are untenable.

In order for a prior art reference to anticipate a claimed compound on the basis that it is inherently produced by a prior art process, the inherency must be certain. *Ex parte Cyba*, 155 USPQ 756 (POBA 1966); *Ex parte McQueen*, 123 USPQ 37 (POBA 1958). Inherency must be a necessary result and not merely a possible result. According to the U.S. Court of Appeals for the Federal Circuit:

> We do not agree that the subject matter of the claim was anticipated. "The mere fact that a certain thing *may result* from a given set of circumstances is insufficient to prove anticipation." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268-69, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)) (emphasis added). EMS was required to prove that an unpressurized flow is necessarily present in the Ruemelin disclosure, and that it would be so recognized by persons of ordinary skill. *Id.* at 1268, 20 USPQ2d at 1749. EMS did not discharge its burden; thus, the district court properly concluded that EMS failed to prove invalidity of claim 20.

Electro Medical Systems S.A. v. Cooper Life Sciences Inc., 32 USPQ2d 1017, 1020 (1994).

In view of this controlling precedent, it is clear that the Examiner has not met his burden of establishing that the claimed invention is anticipated by Everitt *et al.*

Applicants note that new claim 38 is directed to the vector of Claim 25 wherein the vector is a plasmid comprising a cytomegalovirus promoter. Such vectors are clearly not described by Everitt *et al.* whose vector comprises the SV40 promoter.

Since Everitt *et al.* do not disclose a vector capable of transferring genetic material into a human cell wherein the vector encodes an antisense polynucleotide that can bind to human osteonectin mRNA, Everitt *et al.* do not teach every claimed element and cannot anticipate claims 25 and 26.

Applicants assert that the rejection is in error and withdrawal thereof is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1, 6-8, 15-17 and 36 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office action, page 5). Applicants

respectfully traverse the rejection. Applicants incorporate by reference their remarks made in reply to this rejection as set forth in the "Amendment and Reply Under 37 C.F.R. § 1.111" filed June 26, 2001. Applicants also wish to provide the following comments.

In support of the present rejection, the Examiner has referred to a number of documents that allegedly summarise how at the time of the invention *in vivo* antisense therapies were not known. Applicants respectfully disagree that the documents cited by the Examiner represent the state of the art at the time of Applicants' invention.

Applicants respectfully direct the attention of the Examiner to the attached publications by Robinson *et al.*, Dzau *et al.*, Skorski *et al.*, Aoki *et al.* and Georges *et al.* A brief summary of the findings in each of these documents is presented below together with comments on how each supports and enables the claims of the present application.

Robinson *et al.*, *Proc. Natl. Acad. Sci USA* 93:4851-4856 (May 1996) provides a description of the administration of antisense oligodeoxynucleotides (ODNs) that bind to and inhibit VEGF mRNA. The ODNs are injected into the eyes of hyperoxia treated neonatal mice, in order to assess the inhibition of neovascularization of the retina in these animals. The injected ODNs reduced neovascularization by up to 75%, this result being histologically evident in Fig. 5, and is described on page 4853 (column 2, paragraph 3). Hence, Robinson *et al.* show a clear *in vivo* use of antisense ODNs in a pharmaceutical composition to treat neovascularization of the retina.

Dzau *et al.*, *Proc. Natl. Acad. Sci USA 93*:11421-11425 (Oct. 1996) reviews the use of fusigenic viral liposomes in gene therapy, especially for gene therapy in cardiovascular diseases. On page 11422 (column 2, paragraph 1), Dzau *et al.* disclose that a viral liposome vector (HVJ vector) is capable of introducing the human Ducchene muscular dystrophy gene

into mouse muscle cells *in vivo*. On page 11423 (column 1, paragraph 1, last sentence), it is stated that negatively charged HVJ liposomes are most efficient for *in vivo* transfection of liver and skeletal muscle. On this same page, in the fourth paragraph, Dzau *et al.* report that long term *in vivo* gene expression has also been shown for compositions comprising this fusigenic viral liposome. Hence, Dzau *et al* clearly describe a composition suitable for *in vivo* transfection of cells with ODNs or even plasmid vectors.

Aoki *et al.*, *Cancer Res. 55*:3810-3816 (September 1995), describe a liposome-mediated *in vivo* gene transfer of antisense K-*ras* constructs that inhibit the dissemination of pancreatic tumours in mice. On page 3814 (column 2, paragraph 1), Aoki *et al.* state that liposome-mediated *in vivo* gene transfer of the antisense K-*ras* expression plasmid significantly suppressed tumour development. Hence, Aoki *et al.* describe a useful method for transfecting tumour cells *in vivo*.

The use of ODNs directly *in vivo* to treat cancer is also disclosed by Skorski *et al.*, *J. Exp. Med. 182*:1645-1653 (December 1995). On page 1647 (column 1, paragraph 2) Skorski *et al.* demonstrate the antileukemic activities of BCR-ABL and c-*myc* antisense ODNs in SCID mice. The SCID mice were injected intravenously with 10^6 BV 173 cells, a regimen that produces a disease process reminiscent of that in humans. Seven days later the mice were systematically injected for 12 consecutive days with antisense ODNs. Control mice were injected with diluent only. The results of the study are shown on page 1649 (column 1, paragraph 2). Control mice injected with the cancer cells all died within 7 - 10 weeks after injection of the cells. Mice injected with the antisense ODNs survived at least twice and up to four times as long. Hence, Skorski *et al.* disclose a pharmaceutical composition containing antisense ODNs that are useful for the treatment of leukemia *in vivo*.

Finally, Georges *et al.*, *Cancer Res.* 53:1743-1746 (April 1993) describe the intratracheal administration of supernatant containing a retroviral vector comprising antisense K-*ras*, for the treatment of human carcinoma cell growth in mouse lungs. Georges *et al.* describe on page 1744 (column 1, first paragraph of results) a supernatant containing retroviral vectors comprising the K-*ras* antisense sequence that prevented H460a tumour growth in 86-90% of mice innoculated with the tumour cells. The Georges *et al.* study describes the successful *in vivo* use of compositions comprising antisense sequences and retroviral vectors to mediate anti-tumour effects.

The Examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. A specification disclosure which contains a teaching of the manner and process of making and using an invention must be taken as as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is a reason to doubt the truth of the statements contained therein. See M.P.E.P. §2164.04. In view of the positive results obtained by Robinson *et al.*, Dzau *et al.*, Skorski *et al.*, Aoki *et al.* and Georges *et al.*, Applicants submit that the Examiner has not met this burden. In view of the state of the art as exemplified by these publications and the other publications cited in Applicants' "Amendment and Reply Under 37 C.F.R. § 1.111" filed June 26, 2001, when considered with Applicants' specification, it is clear that one of ordinary skill in the art would not doubt that the claimed invention is enabled. Accordingly, the rejection is in error and must be withdrawn. Withdrawal of the rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claims 1 and 6 have been amended as follows:

Please substitute the following claim 1 for pending claim 1:

1. (thrice amended) A [pharmaceutical] composition comprising an inhibitor of human osteonectin and a pharmaceutically acceptable carrier, wherein said inhibitor has an activity selected from the group consisting of: preventing expression of human osteonectin in tumour cells and decreasing expression of human osteonectin in tumour cells, and wherein said inhibitor comprises an antisense polynucleotide which binds to osteonectin mRNA so as to prevent or decrease expression of human osteonectin by preventing or decreasing translation of said mRNA into human osteonectin.

Please substitute the following claim 6 for pending claim 6:

6. (thrice amended) The composition according to Claim [5] 1, wherein said antisense polynucleotide is an antisense RNA complimentary to human osteonectin mRNA.

Claims 37 and 38 are sought to be added.